C-reactive protein with the survival outcomes of bladder cancer patients: a meta-analysis

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Research

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Abstract

Objectives

Accumulating evidences suggested that serum C-reactive protein (CRP) was associated with the survival of bladder cancer patients. However, incongruent findings have been reported.

Methods

We comprehensively searched PubMed, Embase, and Web of science through August 2020 in order to find all eligible studies on the association between CRP and the overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) of bladder cancer patients. The pooled hazard ratios (HRs) together with their 95% confidence intervals (CIs) were estimated by fixed-effect model if the heterogeneity was low, and random-effect model if the heterogeneity was high. A series of subgroup meta-analysis were performed with regard to the specific characteristics of study design.

Results

Thirteen eligible studies were included in this meta-analysis. The pooled results of 8 included studies revealed that an elevated CRP was associated with poor OS (HR = 2.24, 95% CI: 1.16–4.34) and CSS (HR = 1.53 95% CI: 1.36–1.72) of bladder cancer. Besides, the combined results of 3 included studies also indicated an inferior DFS for bladder cancer patients of elevated CRP level (HR = 2.07, 95% CI: 1.24–3.35). Subgroup analyses supported the robust association between elevated CRP and CSS.

Conclusions

These findings suggested that bladder cancer patients reported increase serum CRP had inferior prognostic outcomes.

Background

Bladder cancer is one of the most common cancer worldwide with 549, 393 new cases and 199, 922 deaths in 2018 [1]. Elderly men are predominant in bladder cancer's population with a median age for the primary diagnosis of 73 [2]. Non-muscle invasive bladder cancer (NMIBC) represents 75% of the cases but muscle-invasive bladder cancer (MIBC), which only represents the rest 25%, is more lethal [3, 4]. Many studies have shown that smoking, occupational carcinogen exposure, dietary factors are potential risk factors of bladder cancer [2, 5]. Despite considerable improvement in treatment of bladder cancer in the past decade, investigations on predictive capabilities of survival biomarkers are still of urgent need. It has been consistently mentioned that systemic inflammation plays a central role in cancer's initiation and progression, evidence has also been accumulated in supporting the connection between elevated systemic inflammation level and unfavorable survival of cancer patients [6].

C-reactive protein (CRP) is one of the most representative serum biomarkers for evaluating systemic inflammation [7]. Increased level of CRP has been linked to unfavorable prognosis of many cancers, like colorectal cancer [8], hepatocellular cancer [9], esophageal cancer [10], nasopharyngeal cancer, and cancers of urological system [11]. Several studies have been published in evaluating the prognostic role of CRP in bladder cancer [12–15], although most of them had concluded that elevated CRP was an independent predictor of inferior overall survival (OS) or cancer specific survival (CSS) of bladder cancer patients, studies with insignificant findings also exist.

This incongruity in the association between CRP and the prognosis of bladder cancer indicates the necessity in thoroughly reviewing and synthesizing the results of existing studies. However, to our best knowledge, regarding to this topic, currently no exhaustive meta-analysis has been done. Therefore, the major aim of the current study is to perform a comprehensive meta-analysis regarding to the association between CRP and bladder cancer survival. We intend to simultaneously evaluate the influence of CRP on multiple prognostic outcomes for bladder cancer patients, such as OS, CSS, and disease-free survival (DFS).

Methods

Searching strategy

In accordance with the PRISMA[16], eligible studies have systematically collected from 3 full-text databases (PubMed, Embase, Web of science) before August 11, 2020. We used the following words to preliminarily search for potentially relevant studies in the three databases mentioned above: ("bladder" OR "urothelial" OR "transitional cell") AND ("cancer" OR "tumor" OR "malignancy" OR "carcinoma" OR "neoplasm") AND ("CRP" OR "C-reactive protein" OR "inflammatory markers" OR "inflammatory factors" OR "inflammatory biomarkers") AND ("prognosis" OR "survival" OR "recurrence" OR "progression"). To guarantee the completeness of included studies, the reference lists of all potentially relevant studies were simultaneously checked and searched.

Inclusion and exclusion criteria

Inclusion criteria used to further screen for eligible studies were: (1) cohort design (either prospective or retrospective); (2) investigated the association between serum CRP and bladder cancer outcomes by using Cox proportional hazards model; (3) CRP was dichotomized by using specific cut-offs; (4) report hazard ratios (HRs). The exclusion criteria were: (1) studies of case-control or cross-sectional design; (2) CRP was treated as continuous variable; (3) did not provide HR by using Cox model.

Publication quality assessment

Newcastle-Ottawa Scale (NOS) was used to access the quality of included publications in our study. The scores of NOS were ranged from 0 (lowest score) to 9 (highest score). A study with a NOS score higher than 5 was considered high-quality [17]. We only included studies with NOS scores higher than 5 in this meta-analysis.

Data extraction

First author's name, year of publication, country of origin, type of bladder cancer, cut-off value, HRs with their corresponding 95% confidence intervals (CIs), covariates in multivariate model, and *p*-values were extracted by two investigators independently. The extraction results were compared, and any discrepancy was solved by a third researcher.

Statistical analysis

We used STATA 15.0 software to perform all statistical analyses. The outcomes of interest in the present study were OS, CSS and DFS. The pooled HRs with 95% CIs were used to measure the association between CRP and the survival of bladder cancer patients. I-squared statistic ( ) >50% was used to define the statistical heterogeneity: the fixed-effect model was used when heterogeneity was low, while the random-effect model was used when heterogeneity was high. We performed the subgroup meta-analyses based on the cut-offs of CRP, types of bladder cancer, different sample sizes and origins of the studies. Funnel plot, together with Egger's and Begg's tests were used to test for publication bias.

Results

Study selection

The flowchart for studies selection process was presented in Figure 1. Initially, 683 articles were found after searching in the three databases. Two hundred and four (204) duplicated articles were excluded. For the rest 479 articles, after titles and abstracts review, 406 were further excluded (reasons for exclusion are: not bladder cancer, editorial review, did not analyze CRP, reviews or meta-analysis, published in other languages rather than English, animal studies, conference abstracts, not prognostic studies). Then 73 articles were reviewed in full text to carefully assess the eligibility, 60 of them were further excluded (reasons for exclusion are: other types of urological cancer patients mingled with bladder cancer patients, did not provide measurements of CRP, did not investigate the outcomes of study interest, case-control or cross-sectional design studies, did not use Cox proportional hazards model). In the end, 13 studies were included into our meta-analysis [12–15, 18–26].

Study characteristics

The characteristics of included studies were summarized in Table 1. A total of 3072 patients were analyzed in these 13 studies. The sample size ranged from 34 to 1043. The majority of the patients were men (77%). Nine studies were conducted in Asian countries (5 in Japan, 2 in China, 2 in Korea), and 4 were from European countries (2 in Germany, 1 in Belgium, 1 in the United Kingdom). The age of the patients ranged from 65 to 72 years old, with the medians of follow-up from 7 to 63 months.

CRP with bladder cancer survival

A total of 8 included studies investigated OS, high heterogeneity was observed among them (=97%, < 0.001), therefore a random-effect model was fitted. The pooled results indicated that, an **e**levated CRP was in general associated with poor OS of bladder cancer patients (HR=2.24, 95% CI: 1.16-4.34, *p*=0.017). We also combined studies which reported prognostic significance of CRP in CSS and DFS of bladder cancer by using fixed-effect model, we found that the elevated CRP was also significantly associated with poor CSS (HR=1.53 95% CI: 1.36-1.72, *p*<0.001) and DFS (HR=2.07, 95% CI: 1.24-3.35, *p*=0.005) of bladder cancer (Figure 2).

Considering that different cut-offs of CRP may influence the combined results, we performed a meta-analysis by only including studies which adopted the cut-off of 0.5mg/dl or close. Altogether 6 and 3 studies were combined for CSS and OS, and the results of random-effect models revealed that, an elevated CRP level was only prominently associated with CSS (HR=1.53, 95%CI: 1.26-1.86, *p*<0.001) (Figure 3).

Subgroup analysis

In order to test for robustness of the combined results, we performed a series of subgroup analysis based on different characteristics of included studies for CSS, the most popular outcome of interest among included studies. Different cut-offs for CRP (0.5mg/dl or close VS. 1 mg/dl, Figure 4A), different types of bladder cancer (Unspecified VS. MIBC, Figure 4B), different sample sizes of studies (dichotomized by the mean, <236 VS. ≥236, Figure 4C), different origins of studies (Europe VS. Asia, Figure 4D) were used sequentially to perform subgroup analyses. Results were generally robust with regard to different dichotomization characteristics.

Publication Bias

Begg's and Eggs tests were used to evaluate publication bias. Funnel plots for CSS (Figure 5A), OS (Figure 5B) and DFS (Figure 5C) suggested insignificant publication bias in general.

Discussion

The present meta-analysis has focused on the relationship between CRP and the survival outcomes of bladder cancer. Our results showed that serum CRP is a strong prognostic factor of bladder cancer patients: an elevated serum CRP is significantly associated with inferior OS, CSS, and DFS of bladder cancer. Moreover, among the three survival outcomes that we analyzed, subsequently performed subgroup analyses confirmed a robust association between elevated CRP and CSS, irrespective to the cut-off values, types of bladder cancer, sample sizes, and the origins of the studies.

Inflammation has been identified a major cause of tumor progression [27]. The following underlying mechanisms may be involved. Firstly, inflammatory cells can produce microenvironment for tumor growth, promote angiogenesis and favor neoplastic spread and metastasis [28]. Sui *et al.* in their review noted that inflammatory microenvironment plays a critical role in the initiation and the progression of bladder cancer: pro-inflammatory cells (such as macrophages, suppressor cells, regulatory T cells, dendritic cells, mast cells, neutrophils and lymphocytes) and cytokines (such as tumor necrosis factor-α and interleukins) collectively contribute to bladder cancer formation and progression [29]. Moreover, the disease of cancer itself can initiate a series of systemic inflammatory responses which include hormonal disorder, and changes in blood indicators like CPR, under the influence of neuroendocrine metabolism, hematopoietic function, and energy metabolism [30].

CRP is a highly sensitive biomarker of acute and chronic inflammation [31], and it is easy to measure in clinical practice [32]. After interleukin-6 mediated release by hepatocytes, CRP promotes the proliferation of cancer cells [33]. Therefore, elevated serum CRP goes with the creation of the tumor microenvironment, becomes a critical component of the host's response to the tumor [34]. Shrotriya *et al.* in their systematic review remarked significantly different levels of CRP between cancer patients and the healthy individuals, despite the ambiguity of its etiological role [35]. In addition, several studies have shown a strong relationship between elevated level of CRP with the poor prognosis and the progression of the disease in a variety of malignancies, including urological cancers [35, 36]. CRP level has a significant impact on both NMIBC and MIBC. For NMIBC patients who underwent transurethral resection (TURBT), they have a high risk to progress to MIBC after the treatment [37], and CRP seems participated in that oncologic progression [30]. Moreover, radical cystectomy (RC) is the standard treatment for MIBC, and the CRP level before the surgery was associated with the survival outcome of the patients [3].

Therefore, pre-operative CRP level may to some extent define the eventual prognosis of bladder cancer patients. With this regard, regulate CRP level might be an option to gain survival benefits in this group of patients. Currently, the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COOX-2) inhibitors had already been discussed in cancer chemoprevention studies [38, 39]. Parada *et al.* used rat bladder cancer model to evaluate the effect of celecoxide on COOX-2, and demonstrated that celecoxide had an inhibitory effect on carcinogenesis of bladder cancer, because it significantly reduced the serum CRP level [40]. With regard to the scarcity of available studies, whether the suppression of serum CRP by administrating NSAIDs or COOX-2 inhibitors can exhibit prognosis significance for bladder cancer patients remains unknown, future clinical trials are needed to investigate this important issue.

The current study is the first thorough meta-analysis regarding to CRP and the multiple prognostic outcomes of bladder cancer. Even so, several limitations should be noticed. First of all, in consideration of statistical efficiency, when synthesizing the results, we included as many eligible studies as possible, therefore the heterogeneity of studies is apparent for some pooled estimations. Second, although in the subsequent analyses, we tried to control for heterogeneity by using subgroup analysis, we can only perform subgroup analysis based on very limited characteristics provided by the original studies, the influence of other potential confounding factors could not be effectively discussed.

Conclusion

In summary, this meta-analysis demonstrated that elevated CRP is significantly associated with multiple survival outcomes of bladder cancer patients. This finding suggests that the regulation of serum CRP might be an option for treating bladder cancer patients. Future longitudinal studies of high quality are warranted to corroborate our findings, and to evaluate the prognostic efficacy of CRP regulation treatments.

Abbreviations

CRP: C-reactive protein; OS: overall-survival; CSS: cancer-specific survival; DFS: disease-free survival; NMIBC: non-muscle invasive bladder cancer; MIBC: muscle-invasive bladder cancer; NSAIDs: nonsteroidal anti-inflammatory drugs; COOX-2: cyclooxygenase-2.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated in this analysis are available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YX conceptualized the study. ARD, HR, DF and YC collected and sorted the data. ARD and YX performed data analysis. ARD drafted the manuscript, YX critically revised the paper. All authors read and approved the final manuscript.

Acknowledgments

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, Kiemeney L, Lotan Y, Pang K, Silverman DT, Znaor A, Catto JWF. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. Eur Urol. 2018;74(6):784–95.
3. Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, van Rhijn BWG, Rouprêt M, Shariat SF, Sylvester R, Zigeuner R, Capoun O, Cohen D, Escrig JLD, Hernández V, Peyronnet B, Seisen T, Soukup V. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. Eur Urol. 2019;76(5):639–57.
4. Smith AB, Deal AM, Woods ME, Wallen EM, Pruthi RS, Chen RC, Milowsky MI, Nielsen ME. Muscle-invasive bladder cancer: evaluating treatment and survival in the National Cancer Data Base. BJU Int. 2014;114(5):719–26.
5. Burger M, Catto JWF, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234–41.
6. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochem Pharmacol. 2006;72(11):1605–21.
7. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111(12):1805–12.
8. Shibutani M, Maeda K, Nagahara H, Noda E, Ohtani H, Nishiguchi Y, Hirakawa K. Prognostic significance of the preoperative serum C-reactive protein level in patients with stage IV colorectal cancer. Surg Today. 2015;45(3):315–21.
9. Sieghart W, Pinter M, Hucke F, Graziadei I, Schöniger-Hekele M, Müller C, Vogel W, Trauner M, Peck-Radosavljevic M. Single determination of C-reactive protein at the time of diagnosis predicts long-term outcome of patients with hepatocellular carcinoma. Hepatology. 2013;57(6):2224–34.
10. Guillem P, Triboulet JP. Elevated serum levels of C-reactive protein are indicative of a poor prognosis in patients with esophageal cancer. Dis Esophagus. 2005;18(3):146–50.
11. Dai J, Tang K, Xiao W, Yu G, Zeng J, Li W, Zhang Y-Q, Xu H, Chen Z-Q, Ye Z-Q. Prognostic significance of C-reactive protein in urological cancers: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2014;15(8):3369–75.
12. Tamalunas A, Buchner A, Kretschmer A, Jokisch F, Schulz G, Eismann L, Stief CG, Grimm T. Impact of routine laboratory parameters in patients undergoing radical cystectomy for urothelial carcinoma of the bladder: a long-term follow-up. Urol Int. 2020;104(7-8):551-558.
13. Ma W, Mao S, Bao M, Wu Y, Guo Y, Liu J, Wang R, Li C, Zhang J, Zhang W, Yao X. Prognostic significance of red cell distribution width in bladder cancer. Transl Androl Urol. 2020;9(2):295–302.
14. Nakagawa T, Taguchi S, Uemura Y, Kanatani A, Ikeda M, Matsumoto A, Yoshida K, Kawai T, Nagata M, Yamada D, Komemushi Y, Suzuki M, Enomoto Y, Nishimatsu H, Ishikawa A, Nagase Y, Kondo Y, Tanaka Y, Okaneya T, Hirano Y, Shinohara M, Miyazaki H, Fujimura T, Fukuhara H, Kume H, Igawa Y, Homma Y. Nomogram for predicting survival of postcystectomy recurrent urothelial carcinoma of the bladder. Urol Oncol Semin Orig Invest. 2017;35(7):457.e15-457.e21.
15. Albisinni S, Moussa I, Aoun F, Quackels T, Assenmacher G., Peltier A, Roumeguère T. The impact of postoperative inflammatory biomarkers on oncologic outcomes of bladder cancer. Progr Urol. 2019;29(5):270–81.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med.2009 Jul 21;6(7).
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep;25(9):603–5.
18. Hilmy M, Campbell R, Bartlett JMS, McNicol AM., Underwood MA, McMillan DC. The relationship between the systemic inflammatory response, tumour proliferative activity, T-lymphocytic infiltration and COX-2 expression and survival in patients with transitional cell carcinoma of the urinary bladder. Br J Cancer. 2006;95(9):1234–8.
19. Yoshida S, Saito K, Koga F, Yokoyama M, Kageyama Y, Masuda H, Kobayashi T, Kawakami S, Kihara K. C-reactive protein level predicts prognosis in patients with muscle-invasive bladder cancer treated with chemoradiotherapy. BJU Int. 2008;101(8):978–81.

20. Eggers H, Seidel C, Schrader AJ, Lehmann R, Wegener G, Kuczyk MA, Steffens S. Serum C-reactive protein: A prognostic factor in metastatic urothelial cancer of the bladder. Med Oncol. 2013;30(4):705.
21. Nakata W, Yamamichi G, Tsujimura G, Tsujimoto Y, Nin M, Tsujihata M. Impact of serum sodium concentration on survival outcomes in patients with invasive bladder cancer without metastasis treated by cystectomy. Int J Urol. 2019;26(3):429–31.
22. Kawahara T, Furuya K, Nakamura M, Sakamaki K, Osaka K, Ito H, Ito Y, Izumi K, Ohtake S, Miyoshi Y, Makiyama K, Nakaigawa N, Yamanaka T, Miyamoto H, Yao M, Uemura H. Neutrophil-to-lymphocyte ratio is a prognostic marker in bladder cancer patients after radical cystectomy. BMC Cancer 2016;16:185.
23. Mao SY, Huang TB, Xiong DD, Liu MN, Cai KK, Yao XD. Prognostic value of preoperative systemic inflammatory responses in patients with non-muscle invasive bladder cancer undergoing transurethral resection of bladder tumor. Oncotarget. 2017;8(8):12891–901.
24. Sejima T, Iwamoto H, Masago T, Morizane S, Yao A, Isoyama T, Koumi T, Takenaka A. Effect of pre-operative hematological disorders on cancer-specific survival rate after radical cystectomy for bladder cancer. J Urol. 2013;189(4):e212.
25. Hwang EC, Cho YH, Chung HS, Jung SI, Kang TW, Kwon DD, Kim MK, Kang SG, Kang SH, Cheon J, Ku JY, Ha HK, Jeong CW, Ku JH, Kwak C, Kwon TG, Kim TH, Choi SH, Seo IY. Preoperative systemic inflammatory markers in upper tract urothelial cell carcinoma: Which is better as a prognostic factor? J Urol. 2017;197(4):e874.
26. Ku JH, Kang M, Kim HS, Jeong CW, Kwak C, Kim HH. The prognostic value of pretreatment of systemic inflammatory responses in patients with urothelial carcinoma undergoing radical cystectomy. Br J Cancer. 2015;112(3):461–7.
27. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. Cell. 2010;140(6):883–99.
28. Ridwelski K, Meyer F, Ebert M, Malfertheiner P, Lippert H. Prognostic parameters determining survival in pancreatic carcinoma and, in particular, after palliative treatment. Dig Dis. 2001;19(1):85–92.
29. Sui X, Lei L, Chen L, Xie T, Li X. Inflammatory microenvironment in the initiation and progression of bladder cancer. Oncotarget. 2017;8(54):93279.
30. Yuk HD, Ku JH. Role of Systemic Inflammatory Response Markers in Urothelial Carcinoma. Front Oncol. 2020; 10:1473.
31. Ledue TB, Weiner DL, Sipe JD, Poulin SE, Collins MF, Rifai N. Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. Ann Clin Biochem. 1998;35 (Pt 6):745–53.
32. Siemes C, Visser LE, Coebergh JWW, Splinter TAW, Witteman JCM, Uitterlinden AG, Hofman A, Pols HAP, Stricker BHC. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol. 2006;24(33):5216–22.
33. Trikha M, Corringham R, Klein B, Rossi JF. Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. Clin Cancer Res. 2003;9(13):4653–65.
34. Gakis G. The role of inflammation in bladder cancer. Adv Exp Med Biol. 2014;816:183–96.
35. Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. C-Reactive Protein Is an Important Biomarker for Prognosis Tumor Recurrence and Treatment Response in Adult Solid Tumors: A Systematic Review. PLoS One. 2015;10(12):e0143080.
36. Saito K, Kihara K. C-reactive protein as a biomarker for urological cancers. Nat Rev Urol. 2011;8(12):659–66.
37. Alfred Witjes J, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, Hernández V, Espinós EL, Dunn J, Rouanne M, Neuzillet Y, Veskimäe E, van der Heijden AG, Gakis G, Ribal MJ. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017;71(3):462–75.
38. Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: nested case-control study. Gastroenterology. 2007;133(2):393–402.
39. Basler JW, Piazza GA. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective inhibitors for prostate cancer chemoprevention. J Urol. 2004;171(2 Pt 2): S59-62; discussion S62-63.
40. Parada B, Sereno J, Reis F, Teixeira-Lemos E, Garrido P, Pinto AF, Cunha MF, Pinto R, Mota A, Figueiredo A, Teixeira F. Anti-inflammatory, anti-proliferative and antioxidant profiles of selective cyclooxygenase-2 inhibition as chemoprevention for rat bladder carcinogenesis. Cancer Biol Ther. 2009;8(17):1622–9.

Tables

Table 1 Characteristic of study included in the meta-analysis

Authors, Year	Country	Sample size	Male/ Female	Median follow - up (Months)	Age median	CRP Cut-off value (≥mg/dl)	Survival Analysis	Covariates
M Hilmy,2006	UK	103	70/33	63	NA	1	Univariate/Multivariate	adjuvant therapy
Yoshida, 2007	Japan	88	63/25	33	70	0.5	Univariate/Multivariate	cT stage, cT3/4 vs cT2
Sejima, 2013	Japan	249	214/23	24.8	72	0.5	Univariate/Multivariate	Age, HB, Albumin, T stage, grade, cell type, LVI, LNM, PSM
Hwang,2012	Korea	67	-	10.8	71	1	Univariate	NA
Egger H, 2013	Germany	34	28/6	10.15	66.7	8	Univariate/Multivariate	-
JH Ku,2015	Korea	419	362/57	37.7	65.1	1	Univariate	NA
Kawahara, 2016	Japan	74	56/16	24.2	65	0.08	Univariate/Multivariate	NLR, Pathological Lymph Node Metastasis
Nakagawa,2016	Japan	306	248/58	7	69	0.5	Univariate/Multivariate	Time to recurrence, symptomatic recurrence, Liver metastatic, Serum alkaline phosphatase level, Resection of metastasis, Albumin, Serum
Shi-Yu,2017	China	207	170/37	21	66	0.33	Univariate/Multivariate	Age, Pathologic stage, tumor grade, number of tumors, Postoperative bladder instillation, NLR, PLR, LMR
Nakata, 2018	Japan	179	133/46	50	69	0.5	Univariate/Multivariate	Age, Sex, BMI, cT stage, Grade, Na, LHD, Hb,
Albisinmi,2019	Belgium	134	110/24	21.1	72	0.91	Univariate/Multivariate	NLR, MLR, HPR, locally advanced disease (pT3/4), node positive disease (pN+), age, gender, smoking status, kidney function, , neo-adjuvant therapy
Wen chao Ma, 2020	China	169	145/24	32.32	66.65	0.5	Univariate/Multivariate	Sexe, age, Tstage, N stage, hypertension, Diabetes, Cardiovascular or cerebrovascular diseases, RDW, RBC, Hb, Primary/recurrence,Single/multiple
Tamalunas A, 2020	Germany	1043	793/250	22	70	0.5	Univariate/Multivariate	pT (<3/3–4) pN (0/1) , Prior transfusion, Age, Gender, Cardiac disease, Pulmonary disease , Metabolic disease , Hb

HR: Hazard Ratio, CSS: Cancer Specific Survival, OS: Overall Survival, RFS: Relapse-free survival, DFS Disease-free survival, PFS Progression-free survival, Hb: hemoglobin, NRL: neutrophil-lymphocyte ratio, PRL: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, RBC: red blood cell, RDW: red distribution width, BMI = body mass index, LDH: lactate dehydrogenase, LNM: lymph node metastasis, LVI = lympho-vascular invasion, NA: not available, PS: performance status, PSM: positive surgical margin,

Figures

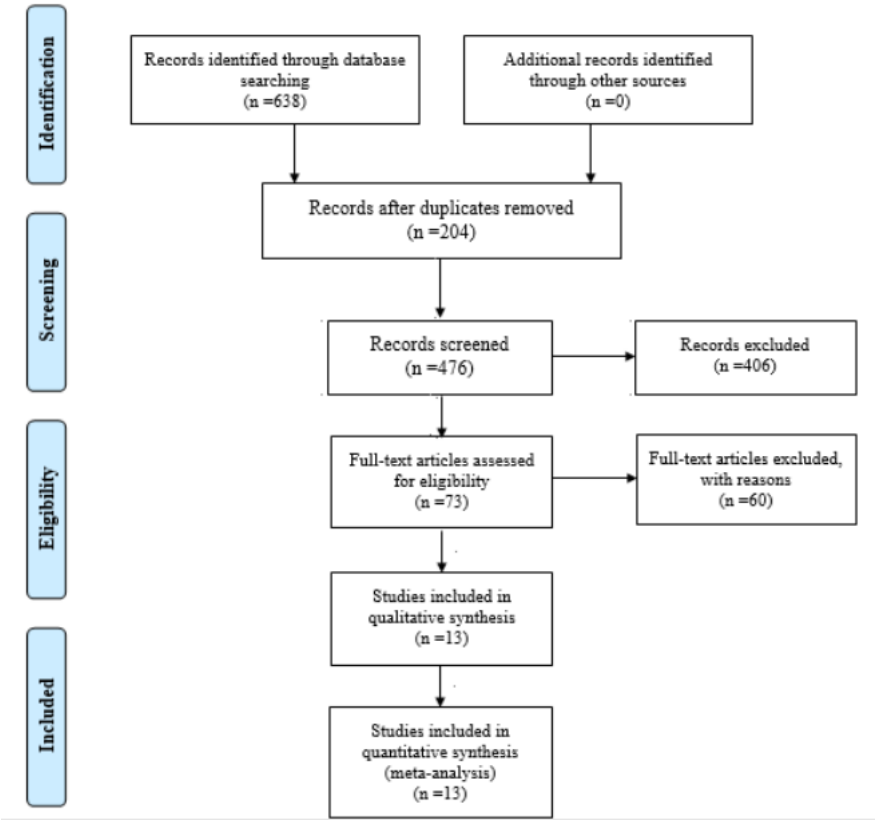


Figure 1

Flowchart for study selection process

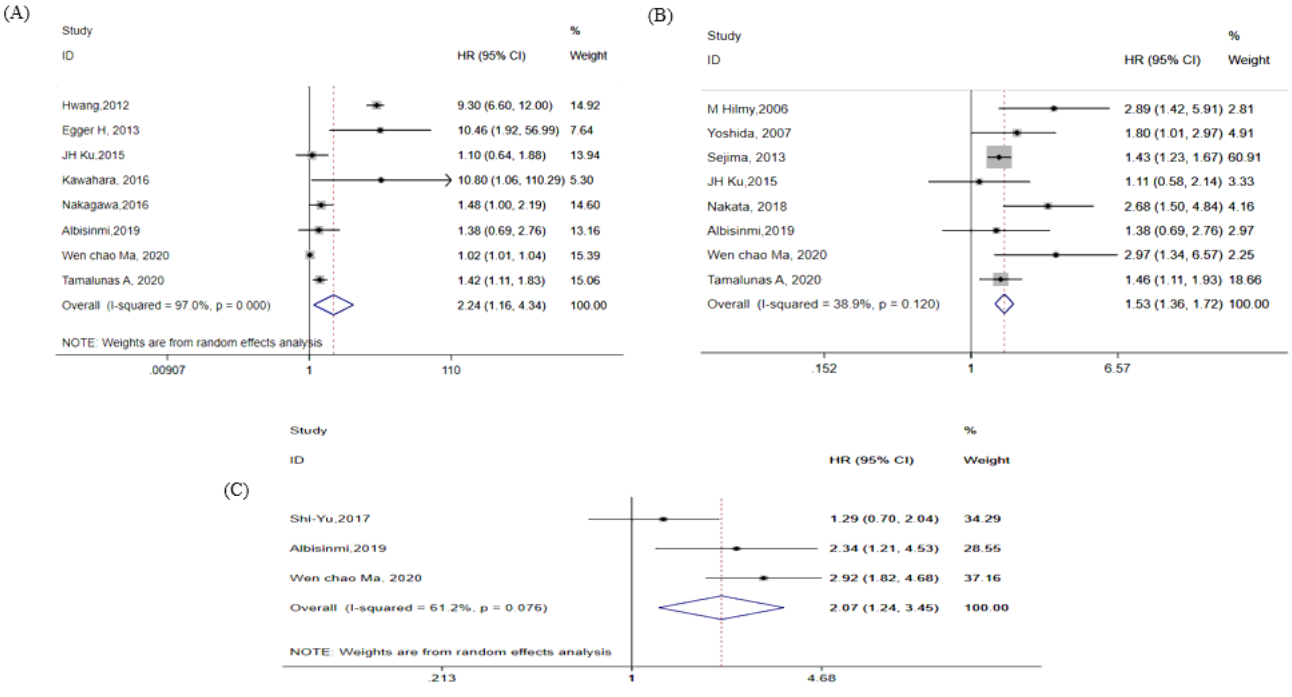


Figure 2

Forest plots for CRP and bladder cancer survival. Panel A represents OS, panel B represents CSS, panel C represents DFS.

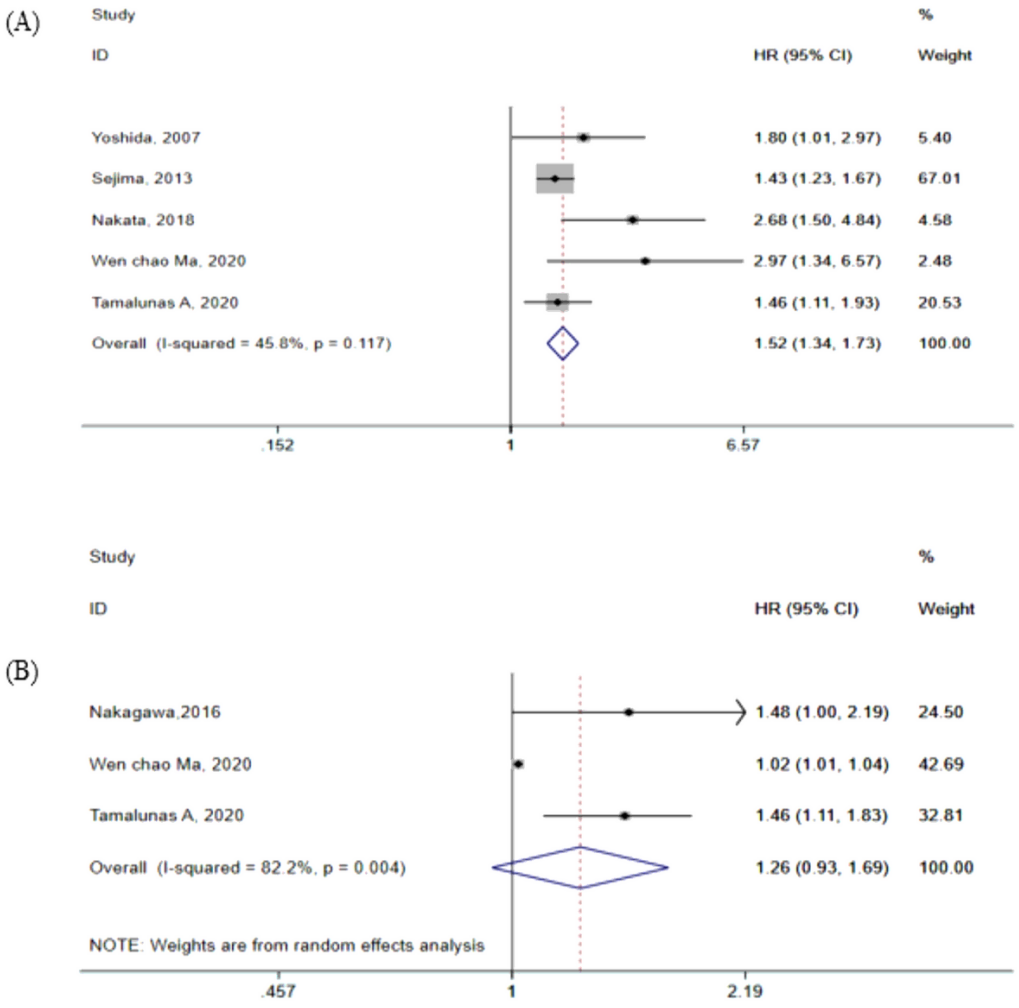


Figure 3

Subgroup meta-analysis for studies adopted CRP cut-off of 0.5mg/L or close. Panel A represents CSS, Panel B represents OS.

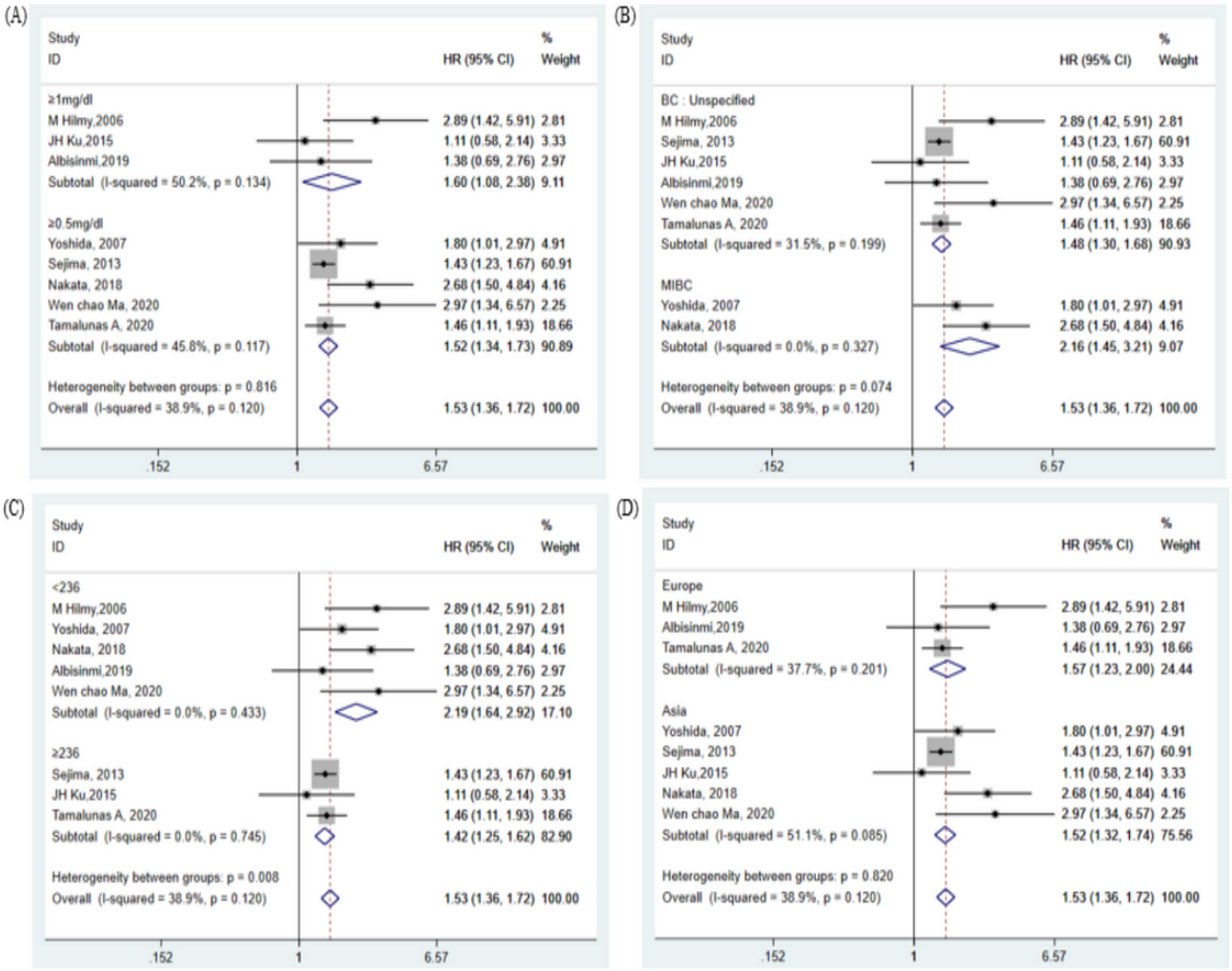
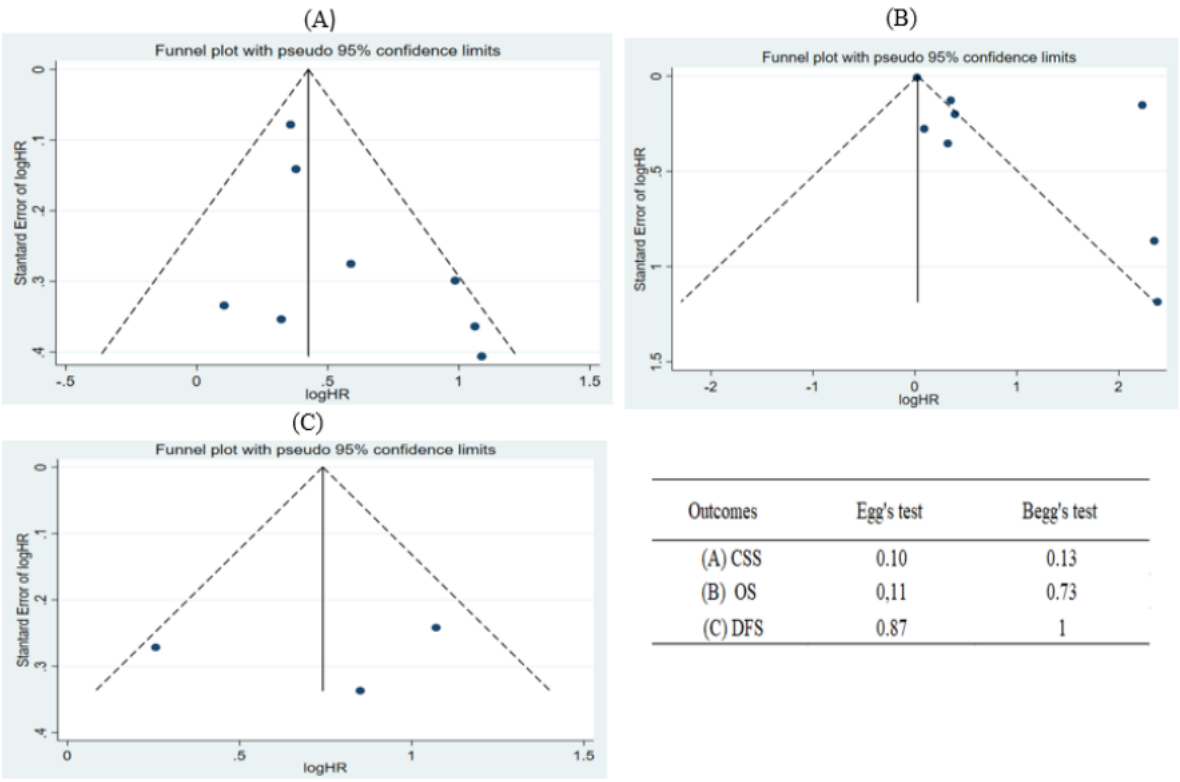


Figure 4

Forest plots of subgroup meta-analysis based on (A) cut-offs of CRP, (B) type of bladder cancer, (C) sample sizes, and (D) origins of the studies



Outcomes	Egg's test	Begg's test
(A) CSS	0.10	0.13
(B) OS	0.11	0.73
(C) DFS	0.87	1

Figure 5

Funnel plot of (A) CSS studies, (B) OS studies and (C) DFS studies